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Editorial Comment

Trickle Down Thrombolysis*

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Assessment of the efficacy of reperfusion strategies for acute myocardial infarction has frequently focused on the restoration of angiographic patency of the infarct-related artery, with intuitive acceptance of the principle that clinical benefit with this form of therapy is linked to the establishment of an open vessel. The Thrombolysis in Myocardial Infarction (TIMI) study group (1) initially proposed the criteria by which angiographic patency after thrombolysis is qualitatively classified according to the extent of penetration of radiographic contrast medium beyond a coronary lesion: grade 0 (no flow), grade 1 (minimal penetration of contrast medium), grade 2 (delayed flow of contrast medium that fills the infarct artery) and grade 3 (brisk and complete filling of the infarct vessel). By convention, arteries with TIMI grade 0 or 1 flow have been regarded as occluded, and those exhibiting grade 2 or 3 flow have been considered to be patent, despite the absence of correlative clinical or myocardial salvage data to support the functional equivalence of TIMI grades 2 and 3 flow.

Recent investigations have in fact challenged the premise that the establishment of TIMI grade 2 flow represents effective recanalization of the infarct-related vessel. Two reports (2,3) have associated the presence of grade 2 flow with an increased risk for reocclusion of the infarct artery in small groups of patients. In an analysis of the Second Multicenter Thrombolysis Trial of Eminase in Acute Myocardial Infarction (TEAM-2), data comparing anistreplase with streptokinase (4), indexes of infarct size (serum cardiac enzyme peaks, time to peak cardiac enzyme levels, and evolution of summed electrocardiographic [ECG] segments) in patients with TIMI grade 2 flow at angiography 90 to 240 min after thrombolysis were comparable to those of patients with TIMI grade 0 or 1 flow but significantly inferior to indexes in patients exhibiting TIMI grade 3 perfusion. Although regional and global left ventricular function were not directly measured in this study, these data suggested that myocardial salvage in the presence of TIMI grade 2 flow may be no better than with an occluded infarct artery.

The present study. In this issue of the Journal, Vogt et al. (5) seek to establish whether early perfusion status of the infarct-related vessel is a valid surrogate end point for clinical outcome after thrombolytic therapy. In doing so, they meaningfully extend previous investigations of the functional adequacy of TIMI grade 2 flow by focusing on mortality, the most fundamental clinical end point. Among this large cohort of patients prospectively enrolled in four German multicenter randomized thrombolytic trials, TIMI grade 2 rather than grade 3 flow at 90-min angiography proved to be a significant predictor of substantially higher risk for in-hospital death (6.6% vs. 2.7%); it is important that the mortality rate among patients with TIMI grade 2 flow was essentially the same as that in patients with occluded (TIMI grade 0 or 1 flow) infarct-related arteries (7.1%). The association between TIMI flow and mortality in this patient group was not confounded by the choice of thrombolytic agent or the use of adjunctive acute coronary angioplasty.

These findings by Vogt et al. (5) have been corroborated by recent preliminary reports by two other groups of investigators. Among >1,200 patients enrolled in five phases of the Thombolysis and Angioplasty in Myocardial Infarction (TAMI) trials (6), TIMI grade 2 rather than grade 3 flow after reperfusion therapy was associated with a greater risk for development of recurrent ischemia or congestive heart failure, diminished salvage of regional and global left ventricular function and a trend toward a higher mortality rate (10.1%, 6.1% or 4.3% among patients with TIMI grade 0/1, 2 or 3 flow, respectively). The TIMI study group (7) examined 154 patients who underwent angiography at 90 min and 18 to 36 h after thrombolysis in the TIMI-4 trial and observed that patients with TIMI grade 2 flow had a threefold greater risk of reocclusion than that of patients with grade 3 flow (15% vs. 5%).

TIMI grade 2 flow: cause or effect? Taken together with the findings of the TEAM-2 (4), TAMI (6), and TIMI (7) study groups, the present analysis by Vogt and associates (5) provides compelling evidence that the patient with TIMI grade 2 rather than complete TIMI grade 3 flow after thrombolysis is at excess risk with respect to nearly every major clinical end point and salvage of left ventricular function. What remains unclear is whether TIMI grade 2 flow is a *cause* or simply a *marker* of adverse outcome. Incomplete patency with TIMI grade 2 flow, whether due to severe residual stenosis, a critical but angiographically inapparent thrombus burden, increased vasomotor arterial tone or distal embolization of thrombin and platelet-fibrin aggregates from the ruptured atherosclerotic plaque, may be inadequate to sustain myocardial viability, thereby resulting in less myocardial salvage. Alternatively, distal TIMI grade 2 blood flow observed by angiography after thrombolysis may simply be a consequence of more extensive myocardial necrosis and edema and represent a relative no-reflow phenomenon. The existence of this lack of reflow phenomenon was elegantly demonstrated in humans in a recent report by

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Table 1. TIMI Grade 2 or 3 Coronary Flow After Thrombolysis for Acute Myocardial Infarction

Trial	Pts (no.)	Thrombolytic Regimen	Time to Angiography (min)	TIMI Grade 3 Flow (%)	TIMI Grade 2 Flow (%)
TAPS (11)	210	Accelerated rt-PA	90	72	12
Neuhaus (10)	74	Accelerated rt-PA	90	78	12
RAAMI (12)	128	Accelerated t-PA	90	62	20
RAAMI (12)	122	Standard t-PA	90	54	23
TAPS (11)	211	Anistreplase	90	54	16
Vogt (5)*	907	Accelerated t-PA, anistreplase, urokinase, r-PA	90	62	14
TAMI (6)	1,229	Standard t-PA, accelerated t-PA, urokinase t-PA + urokinase	90	55	17
TIMI (7)	210	Anistreplase, accelerated t-PA, anistreplase + t-PA	90	47	29
TEAM-2 (4)	359	Anistreplase, streptokinase	90 to 240	56	16
		Pooled		57	17
				(55–59)	(16–18)

*This report is a composite of four different trials (10,11,14,15), two (10,11) of which are included in this table. Data in parentheses indicate confidence intervals. r-PA = recombinant plasminogen activator; RAAMI = Randomized Angiographic Trial of Recombinant Tissue-Type Plasminogen Activator (alteplase) in Myocardial Infarction; TAMI = Thrombolysis and Angioplasty in Myocardial Infarction; TAPS = rt-PA–APSAC (anisoylated plasminogen streptokinase activator) Patency Study; TEAM-2 = Second Multicenter Thrombolysis Trial of Eminase in Acute Myocardial Infarction; TIMI = Thrombolysis in Myocardial Infarction; t-PA = tissue plasminogen activator.

Ito and associates (8). In their study, myocardial contrast echocardiography revealed an absence of tissue level perfusion in 23% of 39 patients with successful recanalization of the infarct-related artery after thrombolysis for anterior myocardial infarction, and the presence of a residual echocardiographic contrast defect was associated with markedly diminished recovery of global and regional left ventricular function.

Interpretation of the clinical relevance of TIMI grade 2 flow after reperfusion therapy is further complicated by the limitations of a static 90-min angiographic view of coronary patency. It is likely that the group of patients exhibiting TIMI grade 2 flow at any instant in time is heterogeneous, encompassing a spectrum of those in whom perfusion of the infarct-related artery is improving along the continuum to TIMI grade 3 flow, as well as patients with extensive myocardial necrosis or edema or unstable lesions prone to reocclusion. These different patient subsets, whose prognoses would be expected to be substantially dissimilar, may be distinguishable by newer technologies with enhanced abilities to assess the stability and true extent of reperfusion, such as contrast perfusion echocardiography or continuous 12-lead digital electrocardiography. Krucoff et al. (9), for example, have shown in a prospective study that the findings of ST segment recovery analysis are actually consistent with infarct vessel *patency* rather than occlusion in >60% of patients with TIMI grade 2 flow after thrombolytic therapy.

Implications for optimal reperfusion. According to the traditional definition encompassing both TIMI grade 2 and grade 3 flow, patency of the infarct-related vessel will be restored by 90 min after initiation of therapy with front-loaded regimens of tissue plasminogen activator (t-PA) in ≥85% of patients with acute myocardial infarction. This seemingly impressive accomplishment has led to a sense of complacency at having attained the ceiling of patency with thrombolytic strategies. It is apparent, however, that TIMI grades 2 and 3 flow are not equivalent in this setting and the achievement of grade 2 reflow does not constitute optimal reperfusion. The relative frequency of grade 2 and 3 flow in coronary arteries considered to be patent after infarction has been remarkably consistent in different reports (Table 1). Among 412 patients in three randomized trials undergoing angiography within 90 min after therapy with rapid dosing of t-PA (10–12), 70% (range 62% to 78%) and 15% (range 12% to 20%) were found to have TIMI grade 3 and grade 2 flow, respectively. The frequency of TIMI grade 3 flow has been substantially lower after treatment with other thrombolytic regimens (range 47% to 62%).

An even more sobering erosion of thrombolytic efficacy is evident when other factors such as early reocclusion are also considered. The authors of the present study (5) recently reported a related analysis of the same patient cohort (13) in which *only 54.7% of patients* were believed to have achieved optimal thrombolysis of the infarct-related artery with t-PA, anistreplase, urokinase or recombinant plasminogen activator by the criterion of TIMI grade 3 flow at 90 min without reocclusion on follow-up angiography 24 to 48 h later. There clearly exists, then, a trickle down phenomenon of levels of coronary patency after thrombolysis for acute myocardial infarction, with the majority of patients failing to achieve optimal reperfusion as progressively more rigorous but relevant criteria are applied.

Conclusions. The investigation by Vogt et al. (5) highlights the deficiency of incomplete reflow and the deceptive nature of a simple angiographic patency measurement for the assessment of thrombolytic efficacy. Complacency with the state of the art of reperfusion therapy is in fact not warranted, and continued efforts will be required to recognize and surmount the inadequacies of present methodologies.

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